Prescribing Information

COUMADIN TABLETS

1. Name of the medicinal product
COUMADIN 1 mg
COUMADIN 2 mg
COUMADIN 2.5 mg
COUMADIN 5 mg

2. Qualitative and quantitative composition
Each tablet of Coumadin 1 mg contains 1 mg warfarin sodium.
Each tablet of Coumadin 2 mg contains 2 mg warfarin sodium.
Each tablet of Coumadin 2.5 mg contains 2.5 mg warfarin sodium.
Each tablet of Coumadin 5 mg contains 5 mg warfarin sodium.

For excipients, see 6.1.

3. Pharmaceutical form
Tablets.

Presentation:
COUMADIN 1 mg tablets are pink, flat capsule shaped, beveled tablets, one side engraved with “WARFARIN” and "TARO", and other side scored and engraved with “1”.

COUMADIN 2 mg tablets are lavender, flat capsule shaped, beveled tablets, one side engraved with “WARFARIN” and "TARO", and other side scored and engraved with “2”.

COUMADIN 2.5 mg tablets are green, flat capsule shaped, beveled tablets, one side engraved with “WARFARIN” and "TARO", and other side scored and engraved with “2½”.

COUMADIN 5 mg tablets are peach, flat capsule shaped, beveled tablets, one side engraved with “WARFARIN” and "TARO", and other side scored and engraved with “5”.

The tablet can be divided into equal halves.

4. Clinical particulars

4.1 Therapeutic indications

COUMADIN is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism.

COUMADIN is indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.

COUMADIN is indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

4.2 Posology and method of administration

The dosage and administration of COUMADIN must be individualized for each patient according to the particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR.

Venous Thromboembolism (including deep venous thrombosis [DVT] and pulmonary embolism [PE])

For patients with a first episode of DVT or PE secondary to a transient (reversible) risk factor, treatment with warfarin for 3 months is recommended. For patients with a first episode of idiopathic DVT or PE, warfarin is recommended for at least 6 to 12 months. For patients with two or more episodes of documented DVT or PE, indefinite treatment with warfarin is suggested. For patients with a first episode of DVT or PE who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions, treatment for 12 months is recommended and indefinite therapy is suggested. For patients with a first episode of DVT or PE who have documented deficiency of antithrombin, deficiency of Protein C or Protein S, or the Factor V Leiden or prothrombin 20210 gene mutation, homocystinemia, or high Factor VIII levels (>90th percentile of normal), treatment for 6 to 12 months is recommended and indefinite therapy is suggested for idiopathic thrombosis. The risk-benefit should be reassessed periodically in patients who receive indefinite anticoagulant treatment. The dose of warfarin should be adjusted to maintain a target INR of 2.5 (INR range, 2.0 to 3.0) for all treatment durations. These recommendations are supported by the 7th ACCP guidelines.

Atrial Fibrillation

Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the American College of Chest Physicians' (ACCP) recommendation that an INR of 2.0-3.0 be used for long term warfarin therapy in appropriate AF patients.

Oral anticoagulation therapy with warfarin is recommended in patients with persistent or paroxysmal AF (PAF) (intermittent AF) at high risk of stroke (i.e., having any of the following features: prior ischemic stroke, transient ischemic attack, or systemic embolism, age >*75* years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus). In patients with persistent AF or PAF, age 65 to 75 years, in the absence of other risk factors, but who are at intermediate risk of stroke, antithrombotic therapy with either oral warfarin or aspirin, 325 mg/day, is recommended. For patients with AF and mitral stenosis, anticoagulation with oral warfarin is recommended (7th ACCP). For patients with AF and prosthetic heart valves, anticoagulation with oral warfarin should be used; the target INR may be increased and aspirin added

depending on valve type and position, and on patient factors.

Post-Myocardial Infarction

The results of the WARIS II study and 7th ACCP guidelines suggest that in most healthcare settings, moderate- and low-risk patients with a myocardial infarction should be treated with aspirin alone over oral vitamin-K antagonist (VKA) therapy plus aspirin. In healthcare settings in which meticulous INR monitoring is standard and routinely accessible, for both high- and low-risk patients after myocardial infarction (MI), long-term (up to 4 years) high-intensity oral warfarin (target INR, 3.5; range, 3.0 to 4.0) without concomitant aspirin or moderate-intensity oral warfarin (target INR, 2.5; range, 2.0 to 3.0) with aspirin is recommended. For high-risk patients with MI, including those with a large anterior MI, those with significant heart failure, those with intracardiac thrombus visible on echocardiography, and those with a history of a thromboembolic event, therapy with combined moderate-intensity (INR, 2.0 to 3.0) oral warfarin plus low- dose aspirin (≤l00 mg/day) for 3 months after the MI is suggested.

Mechanical and Bioprosthetic Heart Valves

For all patients with mechanical prosthetic heart valves, warfarin is recommended. For patients with a St. Jude Medical (St. Paul, MN) bileaflet valve in the aortic position, a target INR of 2.5 (range, 2.0 to 3.0) is recommended. For patients with tilting disk valves and bileaflet mechanical valves in the mitral position, the 7th ACCP recommends a target INR of 3.0 (range, 2.5 to 3.5). For patients with caged ball or caged disk valves, a target INR of 3.0 (range, 2.5 to 3.5*)* in combination with aspirin, 75 to 100 mg/day is recommended. For patients with bioprosthetic valves, warfarin therapy with a target INR of 2.5 (range, 2.0 to 3.0) is recommended for valves in the mitral position and is suggested for valves in the aortic position for the first 3 months after valve insertion.

Recurrent Systemic Embolism and Other Indications

Oral anticoagulation therapy has not been evaluated by properly designed clinical trials in patients with valvular disease associated with atrial fibrillation, patients with mitral stenosis, and patients with recurrent systemic embolism of unknown etiology. A moderate dose regimen (INR 2.0 to 3.0) is recommended for these patients.

An INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

Initial Dosage

The dosing of COUMADIN must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. Lower initiation and maintenance doses are recommended for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR response to COUMADIN. Based on limited data, Asian patients

may also require lower initiation and maintenance doses of COUMADIN. It is recommended that COUMADIN therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations.

Maintenance

Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

If the prescribed dosing regimen requires splitting tablets, it can be done using a dedicated device (tablet splitter).

Duration of Therapy

The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Missed Dose

The anticoagulant effect of COUMADIN persists beyond 24 hours. If the patient forgets to take the prescribed dose of COUMADIN at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Haemorrhagic stroke (see section 4.4 for further details)
- Clinically significant bleeding
- Within 72 hours of major surgery with risk of severe bleeding (for information on other surgery, see section 4.4)
- Within 48 hours postpartum
- Pregnancy (first and third trimesters, see section 4.6)
- Drugs where interactions may lead to a significantly increased risk of bleeding (see section 4.5)

4.4 Special warnings and precautions for use

Most adverse events reported with warfarin are a result of over anticoagulation therefore it is important that the need for therapy is reviewed on a regular basis and therapy discontinued when no longer required.

<u>Commencement of therapy</u>

Monitoring

When warfarin is started using a standard dosing regimen the INR should be determined daily or on alternate days in the early days of treatment. Once the INR has stabilised in the target range the INR can be determined at longer intervals.
INR should be monitored more frequently in patients at an increased risk of over coagulation e.g. patients with severe hypertension, liver or renal disease.
Patients for whom adherence may be difficult should be monitored more frequently.

Thrombophilia

Patients with protein C deficiency are at risk of developing skin necrosis when starting warfarin treatment. In patients with protein C deficiency, therapy should be introduced without a loading dose of warfarin even if heparin is given. Patients with protein S deficiency may also be at risk and it is advisable to introduce warfarin therapy slowly in these circumstances.

Risk of haemorrhage

The most frequently reported adverse effect of all oral anticoagulants is haemorrhage.
Warfarin should be given with caution to patients where there is a risk of serious haemorrhage (e.g. concomitant NSAID use, recent ischaemic stroke, bacterial endocarditis, previous gastrointestinal bleeding).
Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, uncontrolled hypertension, cerebrovascular disease, serious heart disease, risk of falling, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs (see section 4.5). All patients treated with warfarin should have INR monitored regularly. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed on measures to minimise risk of bleeding and to report immediately to physicians signs and symptoms of bleeding.

Checking the INR and reducing or omitting doses depending on INR level is essential, following consultation with anticoagulation services if necessary. If the INR is found to be too high, reduce dose or stop warfarin treatment; sometimes it will be necessary to reverse anticoagulation. INR should be checked within 2–3 days to ensure that it is falling.

Any concomitant anti-platelet drugs should be used with caution due to an increased risk of bleeding.

Haemorrhage

Haemorrhage can indicate an overdose of warfarin has been taken. For advice on treatment of haemorrhage see section 4.9.
Unexpected bleeding at therapeutic levels should always be investigated and INR monitored.

Ischaemic stroke

Anticoagulation following an ischaemic stroke increases the risk of secondary haemorrhage into the infarcted brain. In patients with atrial fibrillation long term treatment with warfarin is beneficial, but the risk of early recurrent embolism is low and therefore a break in treatment after ischaemic stroke is justified. Warfarin treatment should be re-started 2–14 days following ischaemic stroke, depending on the size of the infarct and blood pressure. In patients with

large embolic strokes, or uncontrolled hypertension, warfarin treatment should be stopped for 14 days.

Calciphylaxis

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.

Surgery

For surgery where there is no risk of severe bleeding, surgery can be performed with an INR of <2.5.
For surgery where there is a risk of severe bleeding, warfarin should be stopped 3 days prior to surgery.
Where it is necessary to continue anticoagulation e.g. risk of life-threatening thromboembolism, the INR should be reduced to <2.5 and heparin therapy should be started.
If surgery is required and warfarin cannot be stopped 3 days beforehand, anticoagulation should be reversed with low-dose vitamin K.
The timing for re-instating warfarin therapy depends on the risk of post-operative haemorrhage. In most instances warfarin treatment can be re-started as soon as the patient has an oral intake.

Dental Surgery

Warfarin need not be stopped before routine dental surgery, eg, tooth extraction.

Active peptic ulceration

Due to a high risk of bleeding, patients with active peptic ulcers should be treated with caution. Such patients should be reviewed regularly and informed of how to recognize bleeding and what to do in the event of bleeding occurring.

Interactions

Many drugs and foods interact with warfarin and affect the prothrombin time (see section 4.5). Any change to medication, including self-medication with OTC products, warrants increased monitoring of the INR. Patients should be instructed to inform their doctor before they start to take any additional medications including over the counter medicines, herbal remedies or vitamin preparations.

Thyroid disorders
The rate of warfarin metabolism depends on thyroid status. Therefore patients with hyper- or hypo-thyroidism should be closely monitored on starting warfarin therapy.

Additional circumstances where changes in dose may be required

The following also may exaggerate the effect of warfarin tablets, and necessitate a reduction of dosage:
• Loss of weight
• Acute illness
• Cessation of smoking

The following may reduce the effect of warfarin tablets, and require the dosage to be increased:
• Weight gain
• Diarrhoea
• Vomiting

Other warnings
Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of warfarin are required to achieve the desired anticoagulant effect.

Genetic information

Genetic variability particularly in relation to CYP2C9 and VKORC1 can significantly affect dose requirements for warfarin. If a family association with these polymorphisms is known extra care is warranted.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Warfarin has a narrow therapeutic range and care is required with all concomitant therapy. The individual product information for any new concomitant therapy should be consulted for specific guidance on warfarin dose adjustment and therapeutic monitoring.
If no information is provided the possibility of an interaction should be considered. Increased monitoring should be considered when commencing any new therapy if there is any doubt as to the extent of interaction.

Pharmacodynamic interactions

Drugs which are contraindicated

Concomitant use of drugs used in the treatment or prophylaxis of thrombosis, or other drugs with adverse effects on haemostasis may increase the pharmacological effect of warfarin, increasing the risk of bleeding.
Fibrinolytic drugs such as streptokinase and alteplase are contraindicated in patients receiving warfarin.

Drugs which should be avoided if possible

The following examples should be avoided, or administered with caution with increased clinical and laboratory monitoring:

- Clopidogrel
- NSAIDs (including aspirin and cox-2 specific NSAIDS)
- Sulfinpyrazone
- Thrombin inhibitors such as bivalirudin, dabigatran
- Dipyridamole
- Unfractionated heparins and heparin derivatives, low molecular weight heparins
- Fondaparinux, rivaroxaban
- Glycoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab
- Prostacyclin
- SSRI and SNRI antidepressants
- Other drugs which inhibit haemostasis, clotting or platelet action

Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. Warfarin may initially be given with a heparin in the initial treatment of thrombosis, until the INR is in the correct range.

Metabolic interactions

Warfarin is a mixture of enantiomers which are metabolised by different CYPP450 cytochromes. R-warfarin is metabolized primarily by CYP1A2 and CYP3A4. S-warfarin is metabolised primarily by CYP2C9. The efficacy of warfarin is affected primarily when the metabolism of S-warfarin is altered.
Drugs that compete as substrates for these cytochromes or inhibit their activity may increase warfarin plasma concentrations and INR, potentially increasing the risk of bleeding. When these drugs are co-administered, warfarin dosage may need to be reduced and the level of monitoring increased.
Conversely, drugs which induce these metabolic pathways may decrease warfarin plasma concentrations and INR, potentially leading to reduced efficacy. When these drugs are co-administered, warfarin dosage may need to be increased and the level of monitoring increased.
There is a small subset of drugs for which interactions are known; however their clinical effect on the INR is variable. In these cases increased monitoring on starting and stopping therapy is advised.
Care should also be taken when stopping or reducing the dose of a metabolic inhibitor or inducer, once patients are stable on this combination (offset effect).

Listed below are drugs which are known to interact with warfarin in a clinically significant way.

Examples of drugs which potentiate the effect of warfarin
allopurinol, capecitabine, erlotinib, disulfiram, azole antifungals (ketoconazole, fluconazole etc), omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate, zafirlukast, fibrates, statins (not pravastatin; predominantly associated with fluvastatin), erythromycin, sulfamethoxazole, metronidazole

Examples of drugs which antagonise the effect of warfarin
Barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives, rifampicin, azathioprine, phenytoin

Examples of drugs with variable effect

Corticosteroids, nevirapine, ritonavir

Other drug interactions

Broad spectrum antibiotics may potentiate the effect of warfarin by reducing the gut flora which produce vitamin K. Similarly, orlistat may reduce absorption of vitamin K.
Cholestyramine and sucralfate potentially decrease absorption of warfarin.
Increased INR has been reported in patients taking glucosamine and warfarin. This combination is not recommended.

Interactions with herbal products

Herbal preparations containing St John's Wort (Hypericum perforatum) must not be used whilst taking warfarin due to a proven risk of decreased plasma concentrations and reduced clinical effects of warfarin.
Many other herbal products have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should generally avoid taking any herbal medicines or food supplements whilst taking warfarin, and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

Alcohol

Acute ingestion of a large amount of alcohol may inhibit the metabolism of warfarin and increase INR. Conversely, chronic heavy alcohol intake may induce the metabolism of warfarin. Moderate alcohol intake can be permitted.

Interactions with food and food supplements

Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. Patients should be advised to avoid cranberry products. Increased supervision and INR monitoring should be considered for any patient taking warfarin and regular cranberry juice.
Limited evidence suggests that grapefruit juice may cause a modest rise in INR in some patients taking warfarin.
Certain foods such as liver, broccoli, Brussels sprouts and green leafy vegetables contain large amounts of vitamin K. Sudden changes in diet can potentially affect control of anticoagulation. Patients should be informed of the need to seek medical advice before undertaking any major changes in diet.
There are limited data on possible drug interactions with glucosamine, but increments in the INR parameter have been reported with oral vitamin K antagonists. Patients treated with oral vitamin K antagonists should therefore be closely monitored at the time of initiation or termination of glucosamine therapy.
Many other food supplements have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should generally avoid taking any food supplements whilst taking warfarin, and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

Laboratory tests

Heparins and danaparoid may prolong the prothrombin time, therefore a sufficient time interval should be allowed after administration before performing the test.

4.6. Fertility, pregnancy and lactation

Pregnancy
Based on human experience warfarin causes congenital malformations and foetal death when administered during pregnancy.
Warfarin is contraindicated in pregnancy in the first and third trimester.
Women of child-bearing age who are taking warfarin tablets should use effective contraception during treatment.

Breast-feeding:
Warfarin is excreted in breast milk in small amounts. However, at therapeutic dose of warfarin no effects on the breast-feeding child are anticipated. Warfarin can be used during breast-feeding.

4.7 Effects on ability to drive and use machines
Warfarin has no influence on the ability to drive and use machines.

4.8 Undesirable effects
The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known – cannot be estimated from the available data.

System organ class	Frequency	Adverse Reaction
Infections and infestations	Not known	Fever
Immune system disorders	Not known	Hypersensitivity
Nervous system disorders	Not known	Cerebral haemorrhage; Cerebral subdural haematoma
Vascular disorders	Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Not known	Haemothorax, epistaxis
Gastrointestinal disorders	Not known	Gastroinestinal haemorrhage, rectal haemorrhage, haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena
Hepatobiliary disorders	Not known	Jaundice; hepatic dysfunction
Skin and subcutaneous disorders	Not known	Rash; alopecia; purpura; 'purple toes' syndrome; erythematous swollen skin patches leading to

		ecchymosis, infarction and skin necrosis; calciphylaxis
Renal and Urinary disorders	Not known	Haematuria
Investigations	Not known	Unexplained drop in haematocrit; haemoglobin decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

The benefit of gastric decontamination is uncertain. If the patient presents within 1 hour of ingestion of more than 0.25 mg/kg or more than the patient's therapeutic dose, consider activated charcoal (50 g for adults; 1 g/kg for children)

In cases of life-threatening haemorrhage
Stop warfarin treatment, give prothrombin complex concentrate (factors II, VII, IX, and X) 30–50 units/kg or (if no concentrate available) fresh frozen plasma 15 mL/kg. Discuss with local haematologist or National Poisons Information Service, or both.

Non-life threatening haemorrhage
Where anticoagulation can be suspended, give slow intravenous injection of phytomenadione (vitamin K1) 10–20 mg for adults (250 micrograms/kg for a child)
Where rapid re-anticoagulation is desirable (e.g., valve replacements) give prothrombin complex concentrate (factors II, VII, IX, and X) 30–50 units/kg or (if no concentrate available) fresh frozen plasma 15 mL/kg.
Monitor INR to determine when to restart normal therapy. Monitor INR for at least 48 hours post overdose.

For patients on long-term warfarin therapy without major haemorrhage
• INR >8.0, no bleeding or minor bleeding—stop warfarin, and give phytomenadione (vitamin K1) 0.5–1 mg for adults, 0.015– 0.030 mg/kg (15–30 micrograms/kg) for children by slow intravenous injection or 5 mg by mouth (for partial reversal of anticoagulation give smaller oral doses of phytomenadione e.g., 0.5–2.5 mg using the intravenous preparation orally); repeat dose of phytomenadione if INR still too high after 24 hours. Large doses of phytomenadione may completely reverse the effects of warfarin and make re-establishment of anticoagulation difficult.
• INR 6.0–8.0, no bleeding or minor bleeding—stop warfarin, restart when INR <5.0
• INR <6.0 but more than 0.5 units above target value—reduce dose or stop warfarin, restart when INR <5.0

For patients NOT on long-term anticoagulants without major haemorrhage
Measure the INR (prothrombin time) at presentation and sequentially every 24–48 hours after ingestion depending on the initial dose and initial INR.
• If the INR remains normal for 24–48 hours and there is no evidence of bleeding, there should be no further monitoring necessary.
• Give vitamin K1 (phytomenadione) if:
a) There is no active bleeding and the patient has ingested more than 0.25 mg/kg;
OR
b)The prothrombin time is already significantly prolonged (INR >4.0).
The adult dose of vitamin K1 is 10–20 mg orally (250 micrograms/kg body weight for a child). Delay oral vitamin K1 at least 4 hours after any activated charcoal has been given. Repeat INR at 24 hours and consider further vitamin K1.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmatherapeutic group: Antithrombotic agents, Vitamin K antagonists
ATC code: B01AA03
Mechanism of action
Coumadin is a synthetic anticoagulant of the coumarin series. It acts by inhibiting the formation of active clotting factors II, VII, IX and X.

5.2 Pharmacokinetic properties
Absorption
Coumadin is readily absorbed from the gastro-intestinal tract.
Distribution
Its plasma half-life is about 40 hours.
Biotransformation
It is metabolised in the liver.
Elimination
It is excreted in the urine mainly as metabolites.

5.3 Preclinical safety data
No further data of relevance

6. Pharmaceutical particulars

6.1 List of excipients

COUMADIN Tablets for oral use also contain:

All strengths:	Lactose anhydrous, pregelatinized starch and magnesium stearate
1 mg:	D&C Red No. 6 Barium Lake
2 mg:	FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake
2.5 mg:	FD&C Blue No. 2 Lake and D&C Yellow No. 10 Lake

5 mg:	D&C Red No. 6 Barium Lake and D&C Yellow No. 10 Lake

6.2 Incompatibilities
None

6.3 Expiry date
The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage
Store below 25°C

6.5 Nature and contents of container
HDPE bottles with child-resistant PP cap containing either 30, 100 or 1000 tablets of Coumadin.
Not all packs may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

7. Manufacturer and registration holder
Taro Pharmaceutical Industries Ltd., 14 Hakitor St., Haifa Bay 2624761

8. Marketing authorization numbers
COUMADIN 1 mg tablets: 111.43.29373
COUMSDIN 2 mg tablets: 111.44.29374
COUMADIN 2.5 mg tablets: 111.45.29375
COUMADIN 5 mg tablets: 111.48.29378

Revised in August 2020.